REMARKS

Prior to the present amendment, claims 1, 2, 11, 12, and 34-36 were pending. By this amendment, applicant has amended claims 1 and 36. Accordingly, claims 1, 2, 11, 12, and 34-36 are under examination.

No new matter has been entered by the amendments to the claims.

35 U.S.C. 112, First Paragraph, Rejection

Claim 36 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Prior to the present amendment, claim 36 recited administering "an effective amount of brimonidine tartrate and a dermatologically acceptable carrier to the site of the facial flushing on the human." According to the examiner, the specification and claims as originally filed fail to provide adequate written support for the words: "to the site of the facial flushing," which were previously added to claim 36 by amendment.

Applicant has now amended claim 36 by deleting the words alleged to constitute new matter, and adding the words: "…topically administering a composition comprising an effective amount of brimonidine tartrate and a dermatologically acceptable carrier locally to the facial skin."

Support for the amendment is found in the specification on page 4, lines 18 to 22; page 5, lines 24 to 27; and page 6, lines 1 to 2.

Accordingly, the 35 U.S.C. 112, first paragraph, rejection has been rendered moot.

35 U.S.C. 103 Rejection

The examiner rejected claims 1, 2, 11, 12, and 34-36 under 35 U.S.C. 103(a) as being unpatentable over Wymenga, et al. ("Management of Hot Flushes in Breast Cancer Patients," Acta Oncologia, 41(3), 2002; 269-275) in view of U.S. Patent Publication No. 2003/0229088

to Gil, et al., and further in view of Burke, et al. "Preclinical Evaluation of Brimonidine," Survey of Opthalmology, 41 (Supp.1), 1996, S9-S18) and Dictionary.com ("Topical" and "Transdermal", 2008).

The examiner contends that Wymenga, et al. disclose the treatment of menopausal symptoms, including hot flashes, with clonidine that is administered orally or transdermally. The examiner further contends that one of ordinary skill in the art would have found it obvious to substitute the clonidine of Wymenga, et al. with the brimonidine tartrate compound of Gil, et al. because "the same end result of agonizing the alpha-adrenergic receptors… would have reasonably and predictably resulted." See page 6, middle of first full paragraph of the office action. The examiner further relied upon the Burke reference for disclosing the degree of selectivity of brimonidine for the alpha-2 adrenergic receptor as compared to clonidine. The examiner also relied upon dictionary.com for the definitions of transdermal and topical.

Applicant respectfully disagrees with the examiner's rejection for at least the reasons set forth below.

I. Brimonidine and clonidine are not functionally equivalent for a given condition

Wymenga, et al. disclosed the use of ***clonidine*** for treating menopausal flushing. However, there was no disclosure in Wymenga, et al. of using ***brimonidine*** to treat menopausal flushing.

Gil, et al. disclosed the use of brimonidine and clonidine to treat ***pain***. There is, however, no disclosure in Gil, et al. of treating any condition other than pain. In particular, there is no disclosure in Gil, et al. of treating ***menopausal hot flushes***. It should be noted that menopausal flushing has nothing to do with pain.

Applicant respectfully disagrees with the examiner's statement regarding the equivalence of clonidine and brimonidine for treating hot flushes because both are alpha-2

adrenergic receptor agonists. The examiner's statement is faulty because it assumes that all alpha-2 adrenergic receptor agonists are functionally equivalent for treatment of a particular condition. In fact, all alpha-2 adrenergic receptor agonists are ***not*** functionally equivalent for treatment of a particular condition.

For example, in a section entitled "Systemic therapy" Arndt, et al., the Manual of Dermatologic Therapeutics, Seventh Edition (2007) state the following:

> ***Menopause-related flushing*** or intractable flushing ***might respond*** to low does of clonidine (Catapres), an α-adrenergic agonist, at a dose of 0.05 mg PO b.i.d. or through a tradsdermal patch. It is otherwise apparently ***ineffective in rosacea***. (Emphasis added.)

See page 177, section 2.g of Arndt, et al. (Arndt, et al. has been submitted in a Supplemental Information Disclosure Statement filed herewith.)

According to Arndt, et al., then, the α-adrenergic agonist clonidine has been shown to be ***effective*** for reducing menopausal flushing, but ***ineffective*** for reducing flushing due to rosacea. Therefore, a given α-adrenergic agonist that is useful in reducing redness caused by one condition is not necessarily useful in reducing redness caused by another condition.

By contrast to the ineffectiveness of ***clonidine*** to reduce flushing due to rosacea, ***brimonidine*** has been shown to be effective in reducing redness associated with rosacea in co-owned U.S. Patent No. 7,439,241. It should be noted that brimonidine for reducing redness associated with rosacea is in FDA-regulated clinical trials.

Clonidine and brimonidine are both alpha-2 adrenergic receptor agonists. But clonidine and brimonidine are clearly not functionally equivalent for treating flushing associated with rosacea.

Therefore, all alpha-2 adrenergic receptor agonists are ***not*** functionally equivalent for the treatment of a given condition. Consequently, the examiner is incorrect in stating that:

> The motivation to substitute the alpha-adrenergic agonist clonidine with another known alpha-adrenergic agonist, such as, e.g., brimonidine tartrate, is not based upon alpha-2 adrenoreceptor selectivity, but rather is based upon the common and shared function of simply acting as an alpha-adrenergic agonist.

See office action page 10, middle of first full paragraph. As demonstrated above, there is no such motivation because the function of alpha-adrenergic agonists is not, as the examiner suggests, simple.

In particular, the examiner cites Burke, et al. for disclosing that brimonidine falls within the claimed range of selectivity for the alpha-2 adrenergic receptor. The examiner stated above that the motivation to substitute clonidine with brimonidine is based upon the function of both compounds acting as alpha-adrenergic agonists, not upon alpha-2 adrenoreceptor selectivity. However, applicant is not relying upon the degree of selectivity to distinguish the prior art. Applicant is relying upon the unpredictability of a particular agonist being effective to treat a particular condition.

Accordingly, the examiner's assumption that a person of ordinary skill in the art would predict that a particular alpha-2 adrenergic receptor agonist, e.g., brimonidine, would be as effective for treating a particular condition as another alpha-adrenergic receptor agonist, e.g., clonidine is unfounded. A person of ordinary skill would understand that all alpha-adrenergic receptor agonists do not have the same efficacy for the treatment of a particular condition.

Moreover, it was also demonstrated above that a given α-adrenergic agonist useful in reducing redness caused by one condition is not necessarily useful in reducing redness caused

by another condition. Therefore, it was totally unpredictable that brimonidine would be useful in reducing redness caused by menopausal flushing as presently claimed.

II. The mere fact that both brimonidine and clonidine may both be useful in alleviating pain does not suggest that either is necessarily useful for treating menopause-associated hot flashes

Furthermore, the mere fact that both brimonidine and clonidine may both be useful in alleviating pain does not suggest that either is necessarily useful for treating menopause-associated hot flashes, much less that they are interchangeable for doing so. For example, aspirin and acetaminophen are well-known pain relievers. By analogy to the examiner's argument, acetaminophen could be substituted for aspirin in treating any other condition for which aspirin is useful, including inflammation.

However, acetaminophen cannot be substituted for aspirin to reduce inflammation, because acetaminophen is not known to have an effect on inflammation. The examiner's conclusion that both brimonidine and clonidine are functionally equivalent in reducing redness due to menopause-related hot flashes because both are effective in reducing pain is similarly erroneous.

III. Transdermal administration of a drug is not the same as topical administration of a drug

The examiner contends that the transdermal administration of clonidine disclosed in Wymenga, et al. falls within the scope of the claimed method of topical administration. The examiner concludes "the argument that 'topical' administration as instantly claimed precludes transdermal administration wherein a greater amount of the active agent is absorbed into the bloodstream as disclosed by Wymenga et al. is unpersuasive…" See page 9, first full paragraph, last sentence of the office action. The examiner gives two reasons for this conclusion.

The examiner's first reason is that "neither the specification nor claims as originally filed expressly exclude [transdermal] administration from the scope of the term 'topical administration'…" See page 9, first full paragraph, last sentence of the office action.

However, the specification states:

> The present invention involves local cutaneous application of an effective amount of at least one α_2 adrenergic receptor agonist ***with an ability to act locally*** (emphasis added).

See page 4, lines 18-21 of the application as filed.

A person having ordinary skill understands that transdermal administration is a form of systemic administration. As will be shown below, the specification excludes systemic administration of an α_2-adrenergic receptor agonist, e.g., brimonidine, by requiring that it act locally.

In particular, the specification limits the claimed method to administration of a compound that not only is applied topically. The compound must also act locally.

Applicant has amended claims 1 and 36, the main independent claims, to specify that the agonist acts locally. Therefore, both the claims and the specification distinguish the topical administration of the invention from systemic forms of administration such as transdermal administration as was disclosed by Wymenga.

The examiner's second reason for rejecting the argument that "topical administration as instantly claimed precludes transdermal administration" is that: "Applicant has failed to point to any evidence supporting this alleged fundamental difference between topical and transdermal administration." See page 9, first full paragraph, last sentence of the office action. However, as amended, the claimed method clearly excludes transdermal administration by requiring that the agonist acts locally.

Conclusion

For at least the above reasons, a person having ordinary skill in the art would not understand that clonidine, as taught in the prior art, is the functional equivalent of topical brimonidine, as currently claimed. First, the skilled person would understand from the Burke, et al. reference that brimonidine and clonidine exhibit different selectivity for the alpha-2 adrenergic receptor, and therefore, brimonidine and clonidine exhibit different properties as α_2-adrenergic receptor agonists. Moreover, the skilled person would understand that brimonidine and clonidine are not equivalent for treating flushing due to rosacea, although according to Gil, et al., clonidine are brimonidine are both useful for treatment of pain. Therefore, the skilled person would understand that brimonidine and clonidine are not functionally equivalent α_2-adrenergic receptor agonists for the treatment of any given condition. Finally, a skilled person in the art would not predict that topical brimonidine would be effective for treating menopausal flushing based upon the disclosure that transdermal clonidine is effective for treating menopausal flushing because transdermal administration is systemic, whereas topical administration acts locally.

Applicant respectfully submits that the application is now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to allowance of the application, it is respectfully requested that the examiner contact applicant's attorney at the telephone number provided below.

Respectfully submitted,

_/s/linda d. chin/_____
Linda D. Chin
Registration No.: 58,205
Attorney for Applicant

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
Tel. (516) 822-3550
Fax. (516) 822-3582
LDC/be
306416